About 14 years ago, Kim and Factor reported the first case of HIV-associated pulmonary hypertension [1]. Since then more than 131 cases have been described in the literature [2]. For this reason, HIV-associated pulmonary hypertension has been included as a definite cause of precapillary pulmonary hypertension according to the executive summary of the World Health Organization (WHO) [3]. The incidence of HIV-associated pulmonary hypertension is 1 in 200, much higher than 1 in 200,000 found in the general population [3]. No differences have been found in the clinical, histologic, and hemodynamic features between patients with HIV-associated pulmonary hypertension and HIV-uninfected patients affected by primary pulmonary hypertension.

**Pathogenesis of HIV-Associated Pulmonary Hypertension**

The histopathology of HIV-associated pulmonary hypertension is similar to that of primary pulmonary hypertension. The most common alteration in HIV-associated pulmonary hypertension is plexogenic pulmonary arteriopathy (Fig. 1), while thrombotic pulmonary arteriopathy and pulmonary veno-occlusive disease are more rare histologic findings. This observation may suggest that similar etiopathogenetic mechanisms are at the basis of both HIV-associated pulmonary hypertension and primary pulmonary hypertension.

The finding of an increased incidence of pulmonary hypertension in HIV-infected patients was at first related to viral infection. Although a direct role of HIV-1 in HIV-associated pulmonary hypertension has not been demonstrated [4, 5], several indirect mechanisms may link HIV infection to the pulmonary vascular changes.

**Clinical Manifestations and Diagnosis of HIV-Associated Pulmonary Hypertension**

In the largest clinical series of HIV-associated pulmonary hypertension, 47%–54% of all the patients were male, and the age at the time of diagnosis ranged from 2 to 56 years (mean 33 years). Intravenous drug use was the most common risk factor and ranged from 50% to 58%, while homosexual behavior was present in 20% of the patients, hemophilia in 9%, heterosexual contacts in 9%, and other risk factors in 6% of the patients [2, 12, 13], reflecting the epidemiology of HIV infection in the general population. The mean CD4+ count was 300 mm−3 (range 0–937/mm−3). Currently, no correlation has been found between the CD4+ count and the presence of opportunistic infections and the development of pulmonary hypertension.
<table>
<thead>
<tr>
<th>Pathogenetic hypothesis</th>
<th>Clinical evidence</th>
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<tr>
<td><strong>Cytokines hypothesis (Fig. 2)</strong></td>
<td>Several studies have found an increased production of cytokines [e.g., endothelin-1 (ET-1), interleukin-6 (IL-6), interleukin-1-beta (IL-1β), platelet-derived growth factor (PDGF), and tumor necrosis-factor-alpha (TNF-α)] in patients affected by primary pulmonary hypertension, evoking a potential role of these substances in the pathogenesis of the disease [7–10].</td>
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<td><strong>α1-Adrenergic hypothesis (Fig. 3)</strong></td>
<td>In HIV-infected patients different factors can induce a chronic stimulation of α1-adrenoreceptors of the pulmonary vasculature, including: chronic hypoxia, high circulating levels of norepinephrine, appetite suppressant agents, or cocaine use. The chronic stimulation of pulmonary vascular α1-adrenoreceptors can induce the local production of a large amount of cytokines and in particular of ET-1, IL-1β, IL-6, and PDGF, which in turn stimulate the growth of new pulmonary capillaries, induce vasoconstriction of resistance-sized pulmonary arteries, and have an anti-apoptosis effect [11].</td>
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<td><strong>Toxic substances</strong></td>
<td>Patients with a history of chronic intravenous drug use may develop pulmonary hypertension. Pulmonary artery thrombosis is the main pathological finding in such conditions, and is believed to be due to foreign particle pulmonary emboli, following injections of solutions derived from heroin or from crushed oral medications in which talc was a frequent component [12, 13]. The use of appetite suppressant agents and/or cocaine has been associated with pulmonary hypertension, even in HIV-infected patients, possibly as a consequence of an increased α1-adrenoreceptor stimulation [13, 14].</td>
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<td><strong>Liver disease and HIV-associated pulmonary hypertension</strong></td>
<td>Porto-pulmonary hypertension is now a well-described disease characterized by a clinical and hemodynamic picture substantially identical to primary pulmonary hypertension. In liver cirrhosis, an increased production and a decreased metabolism of some cytokines (e.g., ET-1) have been reported. Kuddus et al. demonstrated that an enhanced synthesis and a reduced metabolism of ET-1 in hepatocytes can be an important mechanism of elevated endogenous and circulating ET-1 in patients affected by liver cirrhosis [15, 16]. Pellicelli et al. reported higher values of systolic pulmonary arterial pressure in HIV-infected patients with HCV/HBV-associated liver cirrhosis compared to other HIV-infected patients without cirrhosis [13].</td>
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<td><strong>Genetic factors (HLA antigens)</strong></td>
<td>In a study conducted by Morse and co-workers, it was found that in ten racially mixed HIV-infected patients with HIV-associated pulmonary hypertension, there was a significant increase in the frequency of human leukocyte antigen (HLA) class II DR52 and DR6, and of the linked alleles HLA-DRB1-1301/2, -DRB3-0301, -DQB1 0603/4, compared to the frequencies of the same alleles in normal Caucasian control subjects [17]. HLA-DR6 and its DRB1-1301/2 subtypes were also significantly increased in HIV-associated pulmonary hypertension patients compared to the respective frequencies of racially diverse HIV-positive control subjects. Furthermore, HLA-DR6 and the DRB1-1301/2 subtype have also been reported to increase in HIV-positive patients who develop diffuse infiltrative lymphocytosis syndrome [18, 19]. It is possible that both entities represent different spectra of a common HLA-DR-determined host response to HIV-1.</td>
</tr>
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</table>
Fig. 2. The possible pathogenetic mechanisms involved in the development of HIV-associated pulmonary hypertension. HIV-infected macrophages, platelets, and lymphocytes may release multifunctional cytokines [endothelin-1 (ET-1), platelet-derived growth factor (PDGF), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α)], which may affect the endothelial cells of the pulmonary vessels, inducing their proliferation and vasoconstriction by a reduction of nitric oxide (NO) production. Moreover, ET-1 produced by endothelial cells may affect the smooth muscle cells of the pulmonary vessels inducing their migration and proliferation. (From [25])

Fig. 3. Chronic stimulation of α1-adrenoreceptors of the pulmonary vasculature can induce the local production of a large amount of cytokines and particularly of ET-1, IL-1β, IL-6, and PDGF, which in turn stimulate the growth of new pulmonary capillaries, induce vasoconstriction of resistance-sized pulmonary arteries, and have an anti-apoptosis effect. (From [26])
The most common presenting symptom was dyspnea (from 49% to 85%), while pedal edema ranged from 11% to 30% of the patients, nonproductive cough from 7% to 19%, syncope from 8% to 12%, and chest pain was present in 7% of the patients. Raynaud’s syndrome, which is more frequently found in patients affected by pulmonary hypertension associated to connective tissue disease, was present in only one patient (1%) [2, 13].

Signs of pulmonary hypertension on physical examination are subtle and often overlooked. An accentuated pulmonary component of the second heart sound, audible at the apex, may be noted in more than 90% of patients, reflecting an increased force of pulmonary valve closure due to elevated pulmonary artery pressure [6]. Other signs of increased pulmonary artery pressure may include the following [6]:

a) An early systolic ejection click due to sudden interruption of pulmonary valve opening
b) A midsystolic ejection murmur caused by turbulent transvalvular pulmonary flow
c) A palpable left parasternal lift produced by the impulse of the hypertrophied high-pressure right ventricle
d) A right ventricular S4 gallop
e) A prominent jugular “a” wave suggesting high right ventricular filling pressure

Physical signs of more advanced disease include the diastolic murmur of pulmonary regurgitation and the holosystolic murmur of tricuspid valve regurgitation, which is audible at the lower left sternal border and augmented with inspiration. A right ventricular S3 gallop, marked distension of the jugular veins, pulsatile hepatomegaly, peripheral edema, and ascites are indicative of right ventricular failure [6].

The principal diagnostic tests used for diagnosis of HIV-associated pulmonary hypertension with related clinical verification are reported in Table 2.

<p>| Table 2. Principal diagnostic tests for diagnosis of HIV-associated pulmonary hypertension |
|----------------------------------------|-----------------------------------------|</p>
<table>
<thead>
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<th>Diagnostic test</th>
<th>Clinical verification</th>
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<td><strong>Laboratory tests</strong></td>
<td>A comprehensive laboratory evaluation which includes complete blood count, prothrombin time, partial thromboplastin time, hepatic profile, autoimmune panel, HIV viral load, HCV antibodies, and HBsAg may be helpful in excluding pulmonary hypertension secondary to systemic diseases. Serum D-dimer, produced during fibrinolysis, if higher than 500 ng/ml may be suggestive of pulmonary thromboembolism.</td>
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<td><strong>Electrocardiogram (ECG) (Fig. 4)</strong></td>
<td>The ECG most often (15%–50%) shows right-axis deviation (S1Q3T3 aspect or McGinn-White sign) along with R&gt;7 mm in V1-V2. Other findings on the ECG include tall, prominent P waves in leads II, III, aVF (secondary to right atrial enlargement), complete or incomplete right bundle branch block, or sinus tachycardia.</td>
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<td><strong>Chest radiogram (Fig. 5)</strong></td>
<td>The chest radiograph frequently has a prominent main pulmonary artery (71%–90%) along with enlarged hilar vessels (80%), “pruning,” or a decrease in peripheral vessels (51%) and cardiomegaly (72%).</td>
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<td><strong>Transthoracic echocardiography (TTE) (Figs. 6–9)</strong></td>
<td>The most frequent findings on TTE are: systolic flattening of the interventricular septum, right atrial and right ventricular enlargement, and tricuspid regurgitation. Additionally, TTE can estimate pulmonary arterial systolic pressure by measuring the Doppler flow through the tricuspid valve according to the modified Bernulli formula: $P = 4V^2$ (where $P$ is pressure gradient and $V$ is peak retrograde velocity). The right atrial pressure is nominally estimated at 10 mmHg. The grade of pulmonary hypertension is categorized as grade I (36–45 mmHg), grade II (46–55 mmHg), and grade III (≥ 56 mmHg). Finally, the TTE can evaluate secondary causes of pulmonary hypertension, such as congenital heart disease or valvular disease.</td>
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cont. →
Treatment of HIV Pulmonary Hypertension

The treatment of HIV-associated pulmonary hypertension is complex and controversial. To date, no controlled clinical trial has evaluated the agent of choice for the treatment of this disease. The principal drugs currently used in the treatment of HIV-associated pulmonary hypertension with related clinical evidence are reported in Table 3.

Conclusions

Pulmonary hypertension associated with HIV infection is a cardiovascular complication that has been recognized with increasing frequency in the last few years. The etiology of HIV-associated pulmonary hypertension is unknown. At present, a multifactorial pathogenesis of HIV-associated pulmonary hypertension has been hypothesized. In this clinical condition, the endothelial dysfunction, the deregulation of circulating cytokines, and genetic factors seem to be implicated in the pathogenesis of this disease. In particular, as in primary pulmonary hypertension, an increase in the plasma concentrations of endothelin-1 (ET-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF)-alpha has been found in patients with HIV-associated pulmonary hypertension. The role of antiretroviral therapy is still being debated. Vasodilator agents such as prostaglandin I2 analog (beraprost) or calcium channel blockers seem to be interesting therapeutic alternatives in the treatment of HIV-associated pulmonary hypertension compared to continuous intravenous infusion of epoprostenol. The use of cGMP-specific phosphodiesterase inhibitors and oral bosentan is promising, but long-term controlled clinical trials are needed in this specific subset of patients.
Table 3. Treatment of HIV-associated pulmonary hypertension

<table>
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<th>Therapy</th>
<th>Clinical evidence</th>
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<td>Highly active antiretroviral therapy (HAART)</td>
<td>Opravil et al. [20] reported that there was a reduction of right systolic ventricular pressure–right atrial pressure gradient in six patients who received antiretroviral treatment compared to seven patients not receiving antiretroviral therapy. All six patients were treated with a single antiretroviral therapy [20]. According to Pellicelli et al., pulmonary hypertension developed in three patients despite HAART and a low HIV viral load [10]. Zuber et al. retrospectively analyzed 47 patients with HIV-associated pulmonary hypertension in the Swiss HIV Cohort Study [21]. According to the data reported by these authors, HAART significantly decreased mortality caused by HIV-associated pulmonary hypertension as well as other causes, suggesting a beneficial effect of HAART in this condition [21].</td>
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<td>Epoprostenol</td>
<td>In a study by Petiprez et al., a short-term treatment with i.v. administered epoprostenol was evaluated in 19 HIV-infected patients with pulmonary hypertension compared to 86 control patients. The proportion of responders to epoprostenol was equal in both groups, and the level of acute pulmonary vasodilatation (percent fall in total pulmonary resistance) achieved with epoprostenol in HIV-infected and non-HIV-infected patients was similar [22]. Aguilar et al. treated six patients with HIV-associated pulmonary hypertension with continuous i.v. infusion of epoprostenol. At 1 year, the mean pulmonary artery pressure and the pulmonary vascular resistance decreased by 21% and 54% with respect to baseline values. They concluded that epoprostenol infusion is effective in improving hemodynamic and functional status acutely as well as in the long term in patients with HIV-associated hypertension [23]. Currently, it is not clear whether early administration of epoprostenol could substantially improve the prognosis of HIV-infected patients with pulmonary hypertension. Epoprostenol therapy is generally limited to seriously ill patients because of its cost and the need for continuous i.v. infusion with associated risk of infection.</td>
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<td>Beraprost</td>
<td>Beraprost can improve the adherence to a long-lasting antiretroviral therapy. Beraprost can be absorbed easily and can be administered in a t.i.d. or q.i.d. fashion. In different studies in non-HIV-associated pulmonary hypertension, the oral administration of beraprost seemed to have beneficial effects on the survival and on the hemodynamic parameters of the patients [13]. Indeed, controlled clinical studies are needed to establish the efficacy of this treatment in HIV-associated pulmonary hypertension.</td>
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<tr>
<td>Bosentan</td>
<td>Bosentan is an endothelin-1 antagonist and may be an effective approach to therapy for pulmonary arterial hypertension [24]. Bosentan increased exercise capacity and improved hemodynamics in patients with primary pulmonary hypertension [24]. However, the therapeutic efficacy of bosentan in patients with HIV-associated pulmonary hypertension needs to be tested in controlled prospective studies.</td>
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<tr>
<td>Calcium channel blockers</td>
<td>Treatment with calcium channel blockers seems to be another alternative in the therapy of HIV-associated pulmonary hypertension. However, reports regarding a small sample of patients with HIV-associated pulmonary hypertension treated with this kind of therapy have shown contrasting response rates [13]. Moreover, calcium channel blockers should be used with caution in patients receiving HAART, since they interact with protease inhibitors.</td>
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<td>Sildenafil</td>
<td>Oral sildenafil seems to be beneficial as a selective pulmonary vasodilator in patients with primary pulmonary hypertension. Sildenafil may preferentially inhibit cGMP-specific phosphodiesterase, which is abundant in lung tissue [13, 22]. Therefore, the possibility of treatment needs to be evaluated prospectively in patients with HIV-associated pulmonary hypertension.</td>
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</table>
HIV-Associated Pulmonary Hypertension

Fig. 4. ECG recording in a patient with HIV-associated pulmonary hypertension. A right-axis deviation ($S_1Q_3T_3$ aspect or McGinn-White sign) along with tall, prominent P waves in leads II, III, aVF (secondary to right atrial enlargement) and complete right bundle branch block is evident.

Fig. 5. Chest radiogram in a patient with HIV-associated pulmonary hypertension. A prominent main pulmonary artery along with enlarged hilar vessels (arrow) accompanied by a decrease in peripheral vessels and cardiomegaly is evident. (From [27])

Fig. 6a-d. Transthoracic echocardiographic findings in HIV-associated pulmonary hypertension. It is possible to observe a systolic flattening of the interventricular septum and right atrial and right ventricular enlargement. (From [27])

Fig. 7. Transthoracic echocardiographic findings in HIV-associated pulmonary hypertension. A systolic flattening of the interventricular septum and right atrial and right ventricular enlargement can be observed.
Fig. 8. Transthoracic echocardiographic findings in HIV-associated pulmonary hypertension. A significant tricuspid regurgitation is observed.

Fig. 9a-d. Transthoracic echocardiographic findings in HIV-associated pulmonary hypertension. The pulmonary arterial systolic pressure can be estimated by measuring the Doppler flow through the tricuspid valve according to Bernulli’s modified formula: $P = 4V^2$ (where $P$ is pressure gradient and $V$ is peak retrograde velocity). The right atrial pressure ($P_{RA}$) is nominally estimated at 10 mmHg.

Fig. 10. Pulmonary angiography in a patient with HIV-associated pulmonary hypertension. It is possible to observe a “pruning” aspect with enlargement of the left pulmonary artery and decrease in peripheral vessels.
References


